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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/758,007	01/10/2001	Leonard I. Zon	701039-50920	8096

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EXAMINER
LI, QIAN J

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 01/17/2003

12

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/758,007	ZON ET AL.	
	Examiner	Art Unit	
	Q. Janice Li	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 October 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-29* is/are pending in the application.

4a) Of the above claim(s) *1-17* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *18-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *11 June 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *7,10* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group VI, claims 18, 19, and 21-29, in Paper No. 10 is acknowledged. The traversal is on the ground(s) that the PTO's position lacking any evidence to support its conclusion", that "screening is not conducted by the positional cloning, but positional cloning is a further step to isolate the gene", that "in order to use positional cloning, one needs the F3 diploid embryo, which has been classified as a separate invention in groups III and IV". This is not found persuasive because claims as written are drawn to different approaches of identifying different genes and the specification presented many different means for identifying a mutant gene, these means include different method steps, such as those recited in claims 8-16, i.e., antibodies detecting different cell cycle proteins, nucleic acids recognizing cell cycle components, flow cytometry, apoptosis markers, irradiation analysis, etc., these methods could be classified as the category of screening for cell proliferation defects, which then properly classified in groups I-III. Claims 7 and 17 (the positional cloning step) depend from claims 1 or 2, and recite one further step in addition to the different steps recited in claims 1 or 2, which presents a completely different approach for identifying a gene, thus, it is distinct from the approaches used in groups I-III that recited by claims 8-16. All of the groups I-IV use either a F2 or F3 diploid embryo as the starting materials, therefore, the related claims have been included in all these groups. Applicants presented similar arguments for groups V and VI, and request to combine

the two groups. Likewise, for the reasons of the foregoing, it is proper to separate the two groups. Therefore it is maintained that each of the Inventions requires a separate search status and distinct consideration. The inventions are mutually exclusive and independent methods for identifying a gene. Groups I-VI are distinct inventions.

The Office also provides evidence to support its position, which will be reiterated as following, "The different methods involve different method steps and different subject for screening. For example, the method steps (e, f, g, h) of groups III & IV are not required in group I & II, or V & VI, the carcinogen used in groups V & VI is not required in groups I-IV, and the positioning cloning step required in groups II, IV, & V is not practiced in other groups. Thus, different methods require distinct technical considerations and search criteria". The searches for groups I-VI would have certain overlap, but they are not co-extensive.

The applicants then cited the following statement of M.P.E.P., "FOR PURPOSES OF THE INITIAL REQUIREMENT, A SERIOUS BURDEN ON THE EXAMINER MAY BE PRIMA FACIE SHOWN IF THE EXAMINER SHOWS BY APPROPRIATE EXPLANATION OF SEPARATE CLASSIFICATION, OR SEPARATE STATUS IN THE ART, OR A DIFFERENT FIELD OF SEARCH AS DEFINED IN MPEP § 808.02", and argue that the different groups all belong to class 435, and subclass 4, 6, 7.1, thus, search for all the groups would nearly co-extensive. In response, the different method holds a separate status in the art, the search for positional cloning is not co-extensive with any of the means recited by claims 8-16, e.g. antibodies detecting different cell cycle proteins, nucleic acids recognizing cell cycle components, flow cytometry, apoptosis markers, irradiation analysis, etc. Therefore, it is maintained that these

inventions are distinct due to their divergent subject matter. Further search of these inventions is not co-extensive. The requirement is still deemed proper and is therefore made **FINAL**.

However, please note that as per Applicants' request and considering issues under 35 USC 112 § 2nd paragraph, two Groups (V and VI) will be rejoined in this application which are not thought to place a serious search burden upon the Office.

Please note that after a final requirement for restriction, the Applicants, in addition to making any response due on the remainder of the action, may petition the Commissioner to review the requirement. Petition may be deferred until after final action on or allowance of claims to the invention elected, but must be filed not later than appeal. A petition will not be considered if reconsideration of the requirement was not requested. (See § 1.181.).

Claims 1-29 are pending, however, claims 1-17 are withdrawn from further consideration by the Examiner, pursuant to 37 CFR 1.142(b), as being drawn to non-elected inventions, there being no allowable generic or linking claim. Claims 18-29 are under current examination.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 18-29 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 18, 19, and 21-29 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: gene-cloning methods, such as positional cloning. The claims provide a method of identifying a gene involved in carcinogenesis, comprising the steps of exposing a fish to a mutagen, mating said fish with a wild-type fish to produce an F1 generation, exposing the eggs of the F1 generation to inactivated fish sperm to create haploid embryos and screening said haploid embryos for cell proliferation defects, mating an F1 generation female harboring a cell proliferation defects with a wild-type fish to produce an F2 generation, and then exposing a wild-type and a member of the F2 generation to a carcinogen, comparing the tumor formation in the wild type or the F2 fishes, wherein an accelerated tumor formation in the F2 generation fish indicates a gene involved in carcinogen. However, the specification fails to teach how to identifying the gene by comparison of the wild-type fish and F2 generation. It appears that a gene has not been identified by the end step of the claim 18, only a fish having at least one mutated gene associated with the tumor formation has been created. Without further pursuing gene cloning methods, such as positional cloning recited in claim 20, a gene could not actually be identified as recited in the preamble of claim 18. Therefore, the claims as written appear to be incomplete.

Claim 25 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. The omitted elements are: the characteristics required for flow cytometry analysis. Claim 25 recites, "the screening is performed using flow cytometry". Flow cytometry is a general tool for measuring many different characteristics of a cell, it is unclear which characteristics the claim embrace, and the metes and bounds of the claim is unclear.

Claim 29 provides a method for haploids screening, but the claim does not set forth any steps involved in the method/process. Method claims need not recite all operating details but should at least recite positive, active steps so that the claims will set out and circumscribe a particular area with a reasonable degree of precision and particularity and make clear what subject matter that claims encompass as well as make clear the subject matter from which others would be precluded, *Ex parte Erlich*, 3 USPQ2d 1011 at 6. In the specification, the only disclosure regarding irradiation is using it as a mutagen (Specification, page 16, lines 15-25). For the purpose of compact prosecution, the claim will be interpreted as using irradiation as a mutagen.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 18-21, 23, 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Spitsbergen et al* (Toxicol Pathol 2000;28:716-725, IDS/CH) in view of *Driever et al* (J Clin Invest 1996;97:1788-94), *Cheng et al* (Biochem Cell Biol 1997;75:525-533) and *Alexander et al* (Dev Genet 1998;22:288-299).

These claims are drawn to a method comprising the steps of exposing a fish to a mutagen, preferably a zebrafish, mating said fish with a wild-type fish to produce an F1 generation, exposing the eggs of the F1 generation to inactivated fish sperm to create haploid embryos and screening said haploid embryos for cell proliferation defects, mating an F1 generation female harboring a cell proliferation defects with a wild-type fish to produce an F2 generation, and then exposing a wild-type and a member of the F2 generation to a carcinogen, comparing the tumor formation in the wild type or F2 fish, wherein an accelerated tumor formation in the F2 generation fish indicates a gene involved in carcinogen; wherein the method further comprising a step of positional cloning of the gene involved in carcinogenesis, wherein the mutation could be induced by exposure to irradiation.

Spitsbergen et al teach investigating the carcinogenesis of certain chemical mutagen in zebrafish, comprising exposing the fish to different dose of a mutagen with different exposure routes (step a or f) and observing the tumor formation in zebrafishes (step g). *Spitsbergen et al* do not teach the process of steps (b) through (e), the irradiation mutation, nor positional cloning.

Driever and Fishman teach the advantage and outlines for using zebrafish for studying heritable disorders, "THE EMBRYO IS TRANSPARENT AND THE FISH IS AMENABLE TO LARGE-SCALE MUTAGENESIS. THUS, GENETIC SCREENS IN THE ZEBRAFISH COULD PROVIDE A 'PHENOTYPE FIRST' APPROACH TO GENE DISCOVERY, COMPLEMENTARY TO 'GENE FIRST' TECHNIQUES..." (left column, page 1788). They teach, "PRODUCE HOMOZYGOUS FISH BY USING GENETICALLY IMPOTENT SPERM TO INDUCE THE MATERNAL CHROMOSOMES OF THE EGG TO COMPLETE MEIOSIS II, WHILE TRANSIENTLY APPLYING PRESSURE TO PREVENT THE FIRST CELL DIVISION" (formation of a haploid embryo, step c, see 1st paragraph, page 1789). They go on to teach the art known technologies for such screening, the first step towards the screens was identifying efficient conditions for mutagenesis, e.g. ENU (single gene mutations) and irradiation (multigenic lesions), and the screens use similar mutagenesis conditions, and breed to homozygosity in a three generation scheme, and identifying the mutant phenotypes with visual inspection under the microscope (steps e & g, see page 1789). They further teach, the screening based on the visually evident phenotype is insufficient for identifying mutations in organs buried deep within the animal, thus, positional cloning as well as biochemical methods could be used for identifying the mutations (antibodies, nucleic acid probes, see last section, page 1792). The outline reviewed by *Driever et al* illustrated the state of the art in using zebrafish for

investigating genes important for vertebrate development and readily applicable for investigating mutagens and carcinogenesis.

Cheng et al detailed using zebrafish in uniparental and two-generation screens for genetic dissection of vertebrate, particularly for assaying recessive mutations (fig. 1). They teach, "IN GYNOGENETIC SCREENS, MENDELIAN INHERITANCE CAN BE PROVEN BY OUTCROSSING F1 FEMALES THAT ARE KNOWN CARRIERS OF INTERESTING MUTATIONS, AND THEN IDENTIFYING THE MUTATIONS IN THE F2 BY CROSSES OF SIBLINGS OR A SECOND ROUND OF HALF-TETRAD ANALYSIS. (steps (b), (c), (f), (g)) THE SAME FRACTIONS OF PRODUCTIVE CROSSES AND MUTANTS WILL BE OBTAINED AS IN TWO-GENERATION CROSSES; THE DIFFERENCE IS THAT THE WORK IS FOCUSED ON *KNOWN CARRIER* FEMALES" (right column, page 530). *Chang et al* teach implicitly but not explicitly screening the haploid embryo.

Alexander et al teach that examining (screening, step d) the molecular markers in the haploid progeny of mosaic F1 females would expedite the screening process (page 293-294).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the methods taught by *Driever et al, Cheng et al, Alexander et al* with the method taught by *Spitsbergen et al* for screening genes involved in carcinogenesis with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to modify the claimed invention because the modified method could expedite the process and discover the dominant and recessive genes as well as influential genes involved in tumorigenesis. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claims 18-24, and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Spitsbergen et al* (Toxicol Pathol 2000;28:716-725, IDS/CH), *Driever et al* (J Clin Invest 1996;97:1788-94), *Cheng et al* (Biochem Cell Biol 1997;75:525-533), and *Alexander et al* (Dev Genet 1998;22:288-299) as applied to claims 18-21, 23, 29 above, and further in view of *Epstein et al* (US 5,756,476).

Claims 22 and 24 are drawn to protein or gene markers that could be used in haploid embryo screening for cell proliferation defects.

Driever et al, Cheng et al, and *Alexander et al* teach screening haploid embryo by a marker, but do not point out the particular markers recited in the claims. However, before the effective filing date of the instant application, the recited markers, such as PCNA and cyclin-b1, and their association with cell proliferation and tumor formation are known in the art and have been used for diagnosis as taught by *Epstein et al* (see abstract, column 2, lines 28-39).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the methods taught by *Spitsbergen et al, Driever et al, Cheng et al, Alexander et al* with the method taught by *Epstein et al* using PCNA and/or cyclin-b1 for haploid embryo screening with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to modify the claimed invention because these markers are known in the art to be associated with proliferation defect and tumor formation. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claims 18-21, 23, 25, and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Spitsbergen et al* (Toxicol Pathol 2000;28:716-725, IDS/CH), *Driever et al* (J Clin Invest 1996;97:1788-94), *Cheng et al* (Biochem Cell Biol 1997;75:525-533), and *Alexander et al* (Dev Genet 1998;22:288-299) as applied to claims 18-21, 23, 29 above, and further in view of *Shyjan et al* (US 6,162,616).

Claim 25 is drawn to a flow cytometry method that could be used in haploid embryo screening for cell proliferation defects.

Driever et al, Cheng et al, and *Alexander et al* teach screening haploid embryo by a marker, but do not point out the particular method for screening. However, before the effective filing date of the instant application, the value of flow cytometry for assaying cell proliferation state and tumor cells are known in the art, as taught by *Shyjan* (see specially column 22, lines 27-39).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the methods taught by *Spitsbergen et al, Driever et al, Cheng et al, Alexander et al* with the method taught by *Shyjan et al* using flow cytometry for haploid embryo screening with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to modify the claimed invention because the method is known in the art for assessing cell proliferation defect and tumor cells. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claims 18-21, 23, 26, 27, and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Spitsbergen et al* (Toxicol Pathol 2000;28:716-725, IDS/CH), *Driever et al* (J Clin Invest 1996;97:1788-94), *Cheng et al* (Biochem Cell Biol 1997;75:525-533), and *Alexander et al* (Dev Genet 1998;22:288-299) as applied to claims 18-21, 23, 29 above, and further in view of *O'Reilly et al* (US 5,854,205).

Claims 26 and 27 are drawn to using apoptosis markers such as TUNEL stain in haploid embryo screening for cell proliferation defects.

Driever et al, Cheng et al, and *Alexander et al* teach screening haploid embryo by a marker, but do not point out the particular markers recited in the claims. However, before the effective filing date of the instant application, the recited marker, e.g. TUNEL stain, and their association with cell proliferation and tumor formation are known in the art, as taught by *O'Reilly et al* (see figs. 8, 12, column 6, lines 12-24).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the methods taught by *Spitsbergen et al, Driever et al, Cheng et al, Alexander et al* with the method taught by *O'Reilly et al* using apoptotic markers for haploid embryo screening with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to modify the claimed invention because these markers are known in the art to be associated with proliferation defect and tumor formation. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claims 18-21, 23, 28, and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Spitsbergen et al* (Toxicol Pathol 2000;28:716-725, IDS/CH), *Driever et al* (J Clin Invest 1996;97:1788-94), *Cheng et al* (Biochem Cell Biol 1997;75:525-533), and *Alexander et al* (Dev Genet 1998;22:288-299) as applied to claims 18-21, 23, 29 above, and further in view of *Li et al* (US 5,679,523).

Claim 28 is drawn to using BrdU staining in haploid embryo screening for cell proliferation defects.

Driever et al, Cheng et al, and *Alexander et al* teach screening haploid embryo by a marker, but do not point out the particular marker BrdU. However, before the effective filing date of the instant application, BrdU as a marker for fast diagnosis of tumor is known in the art, as taught by *Li et al* (column 10, lines 10-15).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the methods taught by *Spitsbergen et al, Driever et al, Cheng et al, Alexander et al* with the method taught by *Li et al* using BrdU assay in haploid embryo screening with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to modify the claimed invention because the marker is known in the art to be associated with proliferation defect and tumor formation. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Q. Janice Li whose telephone number is 703-308-7942. The examiner can normally be reached on 8:30 am - 5 p.m., Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah J. Reynolds can be reached on 703-305-4051. The fax numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of formal matters can be directed to the patent analyst, Dianiece Jacobs, whose telephone number is (703) 305-3388.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235. The faxing of such papers must conform to the notice published in the Official Gazette 1096 OG 30 (November 15, 1989).

Q. Janice Li
Examiner
Art Unit 1632

QJL
January 13, 2003

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER